REMARKS

1. Additional Preliminary Remarks

On page 3, the third full paragraph of the Reply, a typographical error was made with regard to referencing paragraph 0069 rather than paragraph 0043 of the specification. Applicant respectfully requests that the Examiner note that support for vector/probe claims 39-42 can be found at paragraph 0043 of the specification.

2. Additional Patentability Remarks

a. 35 U.S.C. §101

On pages 4-10 of the Office Action, the Examiner rejects claims 31, 32, and 39-42 under 35 U.S.C. §101 for lacking support in the specification for credible utility. As stated in the Reply, the Examiner asserts that the function of SEQ ID NO: 15 as a functional miRNA that targets and modulates expression of a target gene (such as CTSK) must be shown experimentally and states that the experimental evidence that the claimed nucleic acids regulate the asserted target CTSK would be argumentative and requires a declaration.

(1) Applicant Provides Experimental Evidence

In response, Applicant submits herewith the declaration of Dr. Ayelet Chajut, Ph.D. under 37 C.F.R. § 1.132 (the "Chajut Declaration"), which presents experimental evidence that hsa-miR-151 is **naturally expressed**. Furthermore, data presented in the Chajut Declaration show that this miRNA regulates expression of the human target gene CTSK.

The results of these experiments are described in the Chajut Declaration, and are summarized as follows. Dr. Chajut conducted experiments that confirmed that hsa-miR-151 is expressed in Hep3B cells.[1] Microarray experiments show that hsa-miR-151 is expressed at meaningful levels above background.[2] Thus, Applicant submits that these experiments establish that hsa-miR-151 is expressed in Hep3B cells. Additionally, confirmed expression of hsa-miR-151 (GAM1036) as measured by microarray analysis was indicated in the specification as originally filed.[3] Applicant submits that these data show that hsa-miR-151 actually exists.

Dr. Chajut supervised and conducted experiments yielding results that are consistent with an ability of hsa-miR-151 to bind to and regulate the target human CTSK.[4] Specifically, the experiments

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[1] The Chajut Declaration at item 4.

[2] *Id.*

[3] *See* Instant Specification at paragraphs 0278-0281 and Figure 22, lane 15.

[4] *See* the Chajut Declaration at items 5-6.

entailed transfecting an anti-sense oligonucleotide (ASO) specific to hsa-miR-151 into Hep3B cells that express this miRNA, and then comparing the mRNA levels of human CTSK to levels in cells that were not transfected with the ASO.[5] Messenger RNA levels were measured using quantitative reverse transcription polymerase chain reactions ("qRT-PCR") and expressed as a 50-Ct cycle threshold value.[6]

The experiments are based on the following logic: if Hep3B cells do not express hsa-miR-151 and this nucleic acid does not target human CTSK, then one of skill would predict that transfecting Hep3B cells with the ASO would have no effect on human CTSK expression. On the other hand, if Hep3B cells do express hsa-miR-151 and this nucleic acid inhibits expression of human CTSK, then one of skill would expect that transfecting a cell with the anti-hsa-miR-151 ASO would lead to an increase in the level of human CTSK. The experiments described in the Chajut Declaration demonstrate that transfecting Hep3B cells with the ASO results in a 1.8-fold increase at 24 hours and 1.6-fold increase at 48 hours in the level of human CTSK mRNA compared to cells transfected with no ASO.[7] Accordingly, these results are consistent with those one of skill would predict for a cell that expresses hsa-miR-151 and for a miRNA that targets human CTSK mRNA.

(2) ssRNA intermediates

The Examiner further asserts that prior and post-filing art suggests that miRNA target specificity and function depends on the production of a dsRNA intermediate comprising the miRNA. *See* Office Action at page 11, *citing* Cullen, *Viral Research* 102:3-9 (2004)). Applicant respectfully submits that the Examiner has simply identified derivative structures and processes that may be used once an active miRNA has been identified. In this application, Applicant has provided and claimed the key features that provide for regulation of CTSK. As a result, the claimed miRNA sequence (SEQ ID NO: 15) is a subcombination of the miRNA/RISC complex of Cullen. A new product [or process] must be shown to be "operable"—that is, must be "capable of being used to effect the object proposed" in order to meet the utility requirement. *See Mitchell v. Tilghman* 86 U.S. 287 (1873). This does not mean, however, "that a patented device [or composition] must accomplish all objectives stated in the specification. On the contrary, **subcombination** claiming is consistent with the utility requirement of §101 so long as what is described in the claim has utility in itself." *See Carl Zeiss StiftCTSK vs. Renishaw PLC*, 945 F.2d 1173 (Fed. Cir. 1991) (emphasis added). Because Applicant shows the claimed miRNA inhibits CTSK protein expression, the utility flows from this knowledge. In view of the foregoing remarks, Applicant submits

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[5] *See Id.* at item 5.

[6] *See Id.*

[7] *See Id.* at item 6.

that claims 31, 32, and 39-42 have a credible utility due the utility of the subcombination claimed miRNA nucleic acids.

Applicant submits that unlike the facts in *Gazave* (as discussed in the Reply), Dr. Chajut's Declaration validates that Applicant's algorithm does not violate any scientific principles and is wholly consistent with contemporary knowledge regarding miRNA prediction algorithms. In summary, credible utility of the claimed nucleic acids exists after considering the teachings of the specification in combination with Examiner's failure to provide greater than 50% assurance that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility, as well as Applicant's unnecessary step of providing the Examiner with validation results described in the Chajut Declaration. Accordingly, the Examiner has failed to provide by a preponderance of the evidence that Applicant's asserted utility fails. In view of the foregoing remarks, Applicant again requests that the rejection of claims 31, 32, and 39-42 under 35 U.S.C. §101 for lacking credible utility has been overcome and should be withdrawn.

b. 35 U.S.C. §112, First Paragraph (Enablement)

On page 5 of the Office Action, the Examiner maintained the rejection of claims 31, 32, and 39-42 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. The Examiner asserts that since the claimed invention is not supported by a credible asserted utility, one skilled in the art would not know how to use the claimed invention. Applicant respectfully disagrees.

As discussed above, the claimed nucleic acids have a credible, substantial and specific utility, namely in modulating expression of the CTSK transcript, which in turn, may respectfully alter osteoclastic bone resorption. Therefore, Applicant submits that the function of the claimed nucleic acids was known at the time of filing. In view of the foregoing remarks Applicant respectfully requests that the rejection of claims 31, 32, and 39-42 under 35 U.S.C. §112 for lack of enablement has been overcome and therefore should be withdrawn.

3. Conclusion

Applicant request that the declaration and further remarks be made herein into the file history of the application. Upon entry of the amendments specified in the Reply, claims 31, 32, and 39-42 will be pending and under active consideration. Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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